REMARKS

In an Office Action dated April 20, 2007, claims 1-22, all of the claims then pending in the above-identified patent application, were rejected. New claim 23 is being substituted for cancelled claim 1, and is supported at paragraphs 0006, 0011, 0013, 0019, 00020, 0024 and in the Abstract. New claims 24-25 are supported at paragraph 0024. New claims 26-33 also are supported by the above paragraphs. In view of the above amendments, the accompanying Declaration and the following Remarks, Applicants respectfully request reconsideration of this application and allowance of the claims, as amended.

Claims 1-7, 9-15, 19 and 22 have been rejected under 35 USC § 103(a) as being unpatentable over Geistlich et al. US Patent No. 5,837,278 (Geistlich '278), Shimizu U.S. Patent No. 6,090,117, and the abstracts of Hentz et al. and Rosen et al. Claims 1-7 and 9-22 were rejected under 35 U.S.C. §103(a) as being unpatentable over Geistlich et al. in view of Shimizu, and further in view of the abstracts of Hentz et al. and Rosen et al., further in view of Stensaas et al. U.S. Patent No. 4,778,467. Claims 1-15, 19 and 22 were rejected under 35 U.S.C. §103(a) as being unpatentable over Geistlich et al., in view of Shimizu and further in view of the abstracts of Hentz et al. and Rosen et al., further in view of Humes U.S. Patent No. 5,429,938. Insofar as these rejections could apply to the claims, as amended, they are respectfully traversed.

The present claims are directed to a nerve regeneration tube for reconnecting nerve ends, a method for producing such a tube, and a method of reconnecting nerve ends utilizing such a tube. The tube is resorbable and has a resorbable sidewall formed with collagen sheet material having a compact smooth outer barrier surface, and a soft fibrous inner surface opposite the smooth barrier surface. The tube has a compact smooth outer

barrier surface formed with the compact smooth outer barrier surface of the collagen sheet material so as to inhibit cell adhesion thereon and to act as a barrier to prevent passage of cells therethrough. The tube further has a soft fibrous inner surface for promoting nerve growth, the soft fibrous inner surface of the tube being formed with the soft fibrous inner surface of the collagen sheet material. The tube has an inner diameter of about 0.5 – 5 mm, and has opposite tube ends, within which tube ends, during use, are nerve ends for reconnection of the nerve ends, wherein the nerve regeneration tube avoids formation of scar tissue which impairs nerve healing.

In support of patentability of the present invention, submitted herewith is a Declaration of Dr. Myron Spector, one of the inventors in the above-referenced application, and a renowned expert in the field. Dr. Spector has been a Professor of Orthopedic Surgery at Harvard Medical Schools since 1993, and has conducted research on nerve regeneration tubes for over a decade.

As indicated in Dr. Spector's declaration, the surface configuration of tubes defined by the present claims provides such tubes with unexpected properties which could not have been predicted based upon the prior art. As indicated above, Dr. Spector has been researching nerve regeneration tubes for more than a decade. During earlier research that Dr. Spector participated in, comparisons were made between collagen nerve regeneration tubes and silicone nerve regeneration tubes, see, e.g., the papers attached to Dr. Spector's declaration as Exhibit B, Chamberlain et al., Histological response to a fully degradable collagen device implanted in a gap in a rat sciatic nerve, Tissue Engineering, 3,4:353-362, 1997, and Exhibit C, Chamberlain et al., Connective tissue response to tubular implants for peripheral nerve regeneration: the role of myofibroblasts, J. Comp. Neurol. 417:415-430, 2000. The collagen tubes that were used in these earlier studies were obtained from Integra Life Sciences (Integra), Plainsboro, NJ, and are fabricated by freeze-drying Type I

microfibrillar collagen from bovine tendon. The Integra collagen tubes are formed by collagen slurry injection over glass rods, and do not have a soft fibrous inner surface, a fact that Dr. Spector did not consider relevant at the time. In the earlier studies reported in Exhibits B and C, the Integra tubes were compared to silicone nerve regeneration tubes using a severed sciatic nerve rat model. Both studies show that the silicone tubes resulted in substantially greater build-up of fibrous scar tissue within the tubes, as compared to the Integra collagen tubes, with the Exhibit C study indicating that the silicone tubes resulted in formation of a fibrous capsule 10 times thicker than in the Integra collagen tubes. The problem with such fibrous build-up is that this fibrous tissue contains contractile fibroblasts (myofibroblasts) which cause the contracture of the fibrous layer. The contracting fibrous cuff interferes with the elongation of axons through the tube, and thus interferes with nerve regeneration. Although Dr. Spector did not recognize the significance at the time, the silicone tubes have a smoother inner surface than the Integra collagen tubes. Instead, at the time, Dr. Spector and his co-workers noted in the Exhibit C report that: "The differences in connective tissue response between collagen and silicone tubes could have been due to their known differences in chemical composition, permeability, or degradability." Dr. Spector's subsequent research and analysis indicates the thickness of the fibrous scar which forms along the inner surface of the tube is related to the topography of the surface, with smoother surfaces favoring the formation of a thicker scar layer with a great number of contractile cells.

As indicated in Dr. Spector's declaration, the Shimizu patent discloses 3-layer tubes which have smooth collagen or gelatin inner surfaces. Shimizu discloses from column 6, line 48 to column 7, line 50 thereof, formation of a 3-layer collagen tube. A central collagen layer 21 initially is formed on a Teflon rod. This central collagen layer 21 is compressed into a high density, fine fibrous collagen layer, which necessarily and inherently imparts

layer 21 with a smooth interior surface, according to Dr. Spector. After compression, the central layer 21 is removed from the Teflon rod, and the central layer 21 is repeatedly dipped into a hydrochloric acid solution containing collagen, to deposit collagen hydrochloric acid solution layers 22 and 23 on the inner and outer surfaces of the compressed collagen layer 21. According to Dr. Spector, the repeated dipping and drying procedure into collagen hydrochloric acid solution necessarily and inherently forms smooth amorphous inner and outer surface layers 22 and 23 on the compressed central layer 21 of the tube. The same result will necessarily and inherently be obtained if gelatin instead of collagen is utilized for the inner and outer surface layers. Under no conditions disclosed in Shimizu will a soft fibrous inner surface be formed.

As indicated in Dr. Spector's declaration, based on Dr. Spector's studies and experience, the smooth inner surface that will be produced according to the methods of Shimizu will promote formation of a thick layer of fibrous scar tissue on the inner smooth surface of the tube, containing contractile fibroblasts (myofibroblasts) which cause contracture of the fibrous layer and interference with nerve regeneration.

As indicated in Dr. Spector's declaration, the Geistlich et al. patent discloses a resorbable collagen membrane which is surgically inserted around the periphery of a wound cavity to facilitate, e.g., bone regeneration. In view of this reference, when combined with the other applied references, persons of ordinary skill in the art could not have predicted the unexpected results which have been achieved with the present invention, as outlined below.

Attached to Dr. Spector's declaration as Exhibit D is a summary of a study that Dr. Spector was involved in, and which was presented at the 2007 Society for Biomaterials meeting. The Exhibit D study compares results achieved in five groups of animals (Groups I-V) in a rat spinal cord model for nerve regeneration. The study included testing

of the collagen tubes (Groups III and IV) which Dr. Spector and his co-workers fabricated by freeze drying Type I microfibrillar collagen from bovine tendon from Integra, after slurry injection of the collagen over a glass rod mandrel. These tubes do not have a soft fibrous inner surface.

As indicated in Dr. Spector's declaration, the Exhibit D study included testing of BioGide® collagen membrane (Group V) from Geistlich Biomaterials, Wolhusen, Switzerland. This BioGide® collagen membrane material corresponds exactly to the BioGide® collagen sheet material exemplified in the present application and usable in accordance with the present claims. The BioGide® membrane sheet material utilized in Group V of the Exhibit D study has a compact smooth outer barrier surface and a soft fibrous inner surface. In Group V of the Exhibit D study, the tube was formed by wrapping BioGide® membrane sheet material around stump ends of severed spinal nerves, so as to form a nerve regeneration tube as set forth in the present claims, with the soft fibrous surface oriented inwardly toward the severed nerve tissue to form the inner surface of the tube.

As indicated in Dr. Spector's declaration, in the Exhibit D study, the Group V animals with tubes formed of Geistlich BioGide® membrane material having a smooth outer surface and a soft fibrous inner surface, unpredictably had the highest number of axons in the center of the nerve defect, see, Figure 1 in Exhibit D.

As indicated in Dr. Spector's declaration, in the Exhibit D study, the only difference between the Group V animals and the Group IV animals was the structure of the tubular material surrounding the severed nerve tissue. The "dorsal barrier" mentioned in the Exhibit D study refers to a collagen membrane draped over the implant site to assist in preventing overlying tissue (e.g., muscle) from collapsing into the nerve defect.

As indicated in Dr. Spector's declaration, taking into consideration the differences in the tube structure alone, between the Group V and Group IV animals, persons of ordinary skill in the art could not have predicted that the presently claimed invention, utilizing the collagen membrane material of Geistlich et al. U.S. Patent No. 5,837,278 (Group V), could result in the expectedly highest number of center nerve axons among the test animals, as compared to collagen tubes without a soft fibrous inner surface (the Group IV tubes).

As indicated in Dr. Spector's declaration, with reference to Exhibit E attached thereto, Fig. 1 thereof shows a cross-section through the BioGide® collagen membrane material with the compact smooth barrier side at the top, and the soft fibrous side at the bottom. As shown in Fig. 2 of Exhibit E, entubulation of a gap in a rat nerve (spinal cord) with BioGide® demonstrated the absence of a thick fibrous scar on the inner surface of the tube, and demonstrated the ingrowth of cells and tissue into the soft fibrous surface. Based on the prior art, persons of ordinary skill in the art could not have predicted the absence of a thick fibrous scar on the inner surface of a tube according to the present invention, in conjunction with ingrowth of cells and tissues into the soft fibrous inner surface of the tube.

As indicated in Dr. Spector's declaration, the other references cited in the Office Action cannot be combined with Geistlich et al. and Shimizu to render the present claims obvious. Hentz et al. and Rosen et al. both disclose nerve repair wherein a membrane of hypoantigenic collagen (without a soft fibrous inner surface) is wrapped around a nerve. These references are not combinable with the other applied references to render obvious or make predictable the unexpected results achieved with the present invention. Stensaas et al. has no soft fibrous inner surface, and discloses a prosthesis for nerve regeneration which is made of a fluid-impermeable layer composed of silicone, rubber, polyurethane, Teflon or nitrocellulose. Stensaas et al. cannot be combined with the other applied

references to render obvious, or make predictable, the unexpected results achieved with the present invention. Humes does not even relate to nerve regeneration tubes, but instead is directed toward a renal tubule tissue system wherein adult kidney cells are cultured in a medium which may contain Type I collagen and/or Type IV collagen. Humes cannot be combined with the other applied references to render obvious, or make predictable, the unexpected results achieved with the present invention.

In view of the above amendments and remarks, and the Declaration submitted herewith, withdrawal of the rejections based on the references discussed above is respectfully requested.

Applicants submit that the present application is now in condition for allowance. Reconsideration and favorable action are earnestly requested.

Respectfully submitted,

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